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A Comparison of Creatinine, Cystatin C, and Creatinine-Cystatin C Based Equations in HIV/AIDS Patients: A Cross-Sectional Study

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ABSTRACT

Background and Aim: Chronic kidney disease (CKD) is becoming prevalent among people living with HIV/AIDS infection, with kidney dysfunction progressing to end-stage kidney disease (ESKD). We tested the diagnostic performance of creatinine, cystatin c, and the combined (creatinine + cystatin c)-based estimated glomerular filtration rate (eGFR) in assessing kidney dysfunction in HIV/AIDS patients on stable antiretroviral therapy (ART) at the Saltpond District Hospital, Ghana.

Methods: A cross-sectional study of 100 HIV/AIDS patients on ART at the Saltpond District Hospital was conducted. Anthropometric data (height, waist circumference, and weight), blood pressure, and demographic and socioeconomic characteristics were obtained from all enrolled participants through questionnaires. Venous blood was collected for creatinine and cystatin estimation. Urine was also collected and a spot test for micro-albuminuria was performed.

Results: Our study revealed a mean serum creatinine level of 82.60 ± 21.69 with serum creatinine within the normal range for both female and male participants. The eGFR-Scr seems to have a better eGFR/CKD classification performance than the eGFR-Scys-c and eGFR combined (Scr + Scys). At similar cut-off values, eGFR-Scr + Scys showed the greatest diagnostic performance in HIV/AIDS patients, with the largest AUC (AUC = 0.91) in the ROC plot with a sensitivity of 100% and specificity of 11%.

Conclusions: The combined (Scr + Scys) based eGFR equation has the best diagnostic performance in predicting kidney insufficiency/CKD in HIV/AIDS patients on ART. Serum cystatin c-based estimated glomerular filtration (eGFR-Scr) equation is better for assessing kidney function for patients with eGFR< 60 mL/min/1.73 m^2, and eGFR-Scr based equations are better in eGFR/CKD classification and staging.

1 | Background

An estimated 36.7 million people worldwide were living with HIV/AIDS infection in 2016, with almost 25 million people in Sub-Saharan Africa, and about 6.1 million people in Western and Central Africa. As of June 2017, 20.9 million people with HIV/AIDS were receiving antiretroviral therapy (ART) [1]. The introduction of ART has improved survival and reduced

AIDS-related deaths [2]. However, kidney dysfunction is becoming prevalent among HIV/AIDS-infected individuals with progression to end-stage kidney disease (ESKD) [3, 4]. HIV/AIDS infection and ART negatively affect kidney function through the mechanism of drug toxicity which heightens the risk of CKD [5–7].

The impact of HIV/AIDS and chronic diseases on the prevalence of chronic kidney disease (CKD) holds significant public health consequences in Africa [8]. The cost involved in kidney replacement therapy (KRT), the increased risk of mortality, insufficient assets to help patients with established CKD, and its likely effect on medications, are the primary reasons healthcare providers are enthused about early detection of CKD [9]. Therefore, there is a need to accurately and precisely estimate the glomerular filtration rate (GFR) among people living with HIV/AIDS. Some studies have reported an increased risk of kidney disease and reduction of estimated GFR (eGFR) with prolonged ART exposure [10, 11]. A few years past, the two most common methods for assessing kidney function were the Modification of Diet in Renal Disease (MDRD) equation, and the Cockcroft–Gault equation [12]. In recent times, the creatinine CKD-EPI equation has proven more accurate than the MDRD equation for estimating GFR, hence, it has surpassed the MDRD equation as the method of choice in GFR estimation in many laboratories [13].

Serum creatinine is however affected by muscle mass and tubular secretion [14]. Again, antiretroviral drugs like cobicistat, dolutegravir, and many others are known inhibitors of proximal tubular creatinine secretion (IPTCrS). When serum creatinine is used to assess glomerular function in individuals using these drugs, we expect an increase in serum creatinine while eGFR decreases [15]. More recently serum cystatin C-based eGFR estimation has emerged as having a better GFR estimation and better diagnostic performance than creatinine-based eGFR equations [16, 17]. cystatin C is a low molecular weight protein produced by all nucleated cells, easily filtered by the glomerulus, and broken down in the proximal tubule [14, 18]. Cystatin is also affected by inflammation, steroid use, and adiposity [18], making it a less reliable marker for GFR estimation in certain patient populations [18–20]. Inker et al. [21] demonstrated in their study that a combined (creatinine + cystatin c) CKD-EPI equation provided a more precise estimation of GFR than the creatinine or cystatin-based CKD-EPI equation.

Given the inherent limitations of both assays, the combined equation leverages the strengths of both markers, reducing biases and improving early detection of kidney dysfunction. As patients with HIV/AIDS infection are prone to developing CKD, it is essential that eGFR equations precisely and accurately evaluate GFR and recognize patients with possible CKD. Thus, we assessed the diagnostic performance of creatinine-based eGFR, cystatin c-based eGFR and combined (creatinine+cystatin c) eGFR equations in diagnosing kidney insufficiency in HIV/AIDS patients on stable ART at the Saltpond District Hospital, Ghana.

2 | Methods

2.1 | Study Design/Study Site

This study utilized a cross-sectional design to evaluate the diagnostic performance of eGFR-creatinine, eGFR-cystatin C, and eGFR combined (creatinine+cystatin C) based equations among HIV/AIDS patients visiting the Saltpond District Hospital. The hospital, a primary facility, is located at Saltpond in the Mfantseman District in the Central region of Ghana. It has an outpatient department and provides medical, surgical, obstetrics and gynecology, pediatric, X-ray, and laboratory services. It also has an ART clinic which caters for people living with HIV/AIDS.

2.2 | Study Population/Ethical Clearance

We determined the sample size using Cochran's sample size formula ($N = Z^2p[1-p]/d^2$). We used a confidence interval constant (Z) of 1.96, a population prevalence (p) of 1.6% [22], and a percentage margin of error (d) of 5%. We had an estimated sample size of (N) of 24. To increase the statistical power of our study and enhance the generalizability of our findings, we adjusted the sample size to 100. We recruited 100 HIV (I and II) positive patients (confirmed with Oraquick) who were 18 years and above and on ART for the study. Data were collected from all participants who consented to the study. We excluded HIV/AIDS patients who had hypertension, diabetes mellitus, or malignancy before the diagnosis. Ethical approval was obtained from the Cape Coast Teaching Hospital Institutional Review Board and informed written consent was also obtained from the participants. The ethical clearance ID for the study was CCTHERC/RS/EC/2017/13.

2.3 | Blood Sample Collection and Biochemical Analysis

Eligible participants provided 5 mL of venous blood into serum separator tubes, which was left to clot, and then centrifuged at 3000 rpm for 3–5 min within 30 min of sample collection. Creatinine was measured using the kinetic-modified Jaffe method [23]. Absorbance was read using the spectrophotometer at wavelength 500 nm. Creatinine concentration was calculated as:

$$\text{Creatinine concentration } (\mu\text{mol/L}) = \frac{\text{Absorbance (Test)}}{\text{Absorbance (Standard)}} \times \text{Conc. of standard } (\mu\text{mol/L}).$$

Serum cystatin was measured using Human Cystatin C ELISA kit [24]. A sterile container was given to patients and instructions on accurate urine sample collection were given to them for urine sample collection for the estimations of urine microalbumin. Microalbumin was assessed using the Rapid Response Microalbumin 2-1 Combo Strip.

2.4 | Statistical Analysis

The data were analyzed using the Statistical Programme for Social Sciences 11.0 (SPSS 11.0) for Windows (SPSS Inc. Chicago, 16). The median with IQR was obtained for non-parametric data and the mean with SD was obtained for continuous data. Linear regression between eGFR-cystatin C and/or eGFR-creatinine and serum creatinine and serum cystatin c was performed on data collected. The Bland–Altman plot was used to provide insights into the level of agreement between the different equations. The receiver operating characteristic curve (ROC) with area under the curve (AUC) graph representation was used to assess the diagnostic accuracy of different eGFR equations. A *p*-value of equal to or less than 0.05 ($p \leq 0.05$) was considered statistically significant. All statistical analyses were pre-specified in the study's statistical analysis plan. All tests were two-sided except for the ROC analysis, which was performed as a one-sided test to evaluate the hypothesis that the combined eGFR equation (eGFR-SCr + SCys) would have greater diagnostic accuracy.

3 | Results

Table 1 presents kidney function and eGFR of patients according to the eGFR-Scr, eGFR-Scys, and eGFR-Scr + Scys equations. The mean serum creatinine concentration was significantly higher in males than in females ($p = 0.006$). The median eGFR (sCys) was 204.18 (41.5) and was significantly higher in males than in females ($p = 0.03$).

Table 2 shows the classification of eGFR/CKD staging with eGFR-SCr, eGFR-Scys, and the eGFR combined SCr + SCys equations. The eGFR-Scr + Scys classified a higher percentage (91%) of patients in G1 and was able to stage participants in G1, G2, G3a, and G3b with the absence of G4 staging. The eGFR-Scys classified 90% in G1 but was able to stage patients to G1, G2, and G4 with no G3a and G3b staging. The eGFR-Scr had the lowest percentage 62% of patients in G1. However, it presented patients in G1, G2, G3a, and G4 but without G3b eGFR classification.

TABLE 1 | Renal function and eGFR of HIV patients on ART according to different CKD-EPI equations.

	Total	Male	Female	*p*-value
Urea (mmol/L)	3.00 (1.0)	2.5 (2.0)	3.00 (1.0)	0.962
ACR (mg/g)	77.50 (90.0)	75.0 (80)	77.50 (86)	0.899
S-creatinine (μmol/L)	82.60 ± 21.69	91.38 ± 22.14	80.85 ± 21.44	0.006
S-cystatin C (mg/L)	1.02 (0.37)	1.03 (0.23)	1.01 (0.38)	0.622
eGFR-Scr (mL/min/1.73 m²)	98.15 ± 29.04	110.38 ± 26.20	95.70 ± 28.06	0.640
eGFR-Scys (mL/min/1.73 m²)	204.18 (41.5)	215.8 (28.22)	199.2 (46.48)	0.027
eGFR-Scr + Scys (mL/min/1.73 m²)	185.92 (58.1)	209.16 (38.18)	185.92 (53.12)	0.146

Results are presented as median (inter-quartile range) and all others as mean±standarad deviation.
Abbreviations: ACR = albumin to creatinine ratio; eGFR = estimated glomerular filtration rate; eGFR-Scr = estimated glomerular filtration rate-serum creatine; eGFR-Scys = serum cystatin; eGFR-Scr + Scys = estimated glomerular filtration rate-serum creatinine + Serum cystatin.

TABLE 2 | Classification of eGFR/CKD stages of HIV patients on ART according to serum cystatin, serum creatinine, and combined serum cystatin/serum creatinine equations.

Stages	eGFR-Scr	eGFR-Scys	eGFR-Scr + Scys
eGFR (mL/min/1.73 m²)			
≥ 60	83 (92.2)	81 (90.0)	84 (93.3)
< 60	7 (7.8)	9 (10.0)	6 (6.7)
eGFR staging, *n* (%)			
G1: ≥ 90	56 (62.2)	81 (90.0)	82 (91.2)
G2: 60–89	28 (31.1)	2 (2.2)	2 (2.2)
G3a: 45–59	4 (4.4)	0 (0.0)	2 (2.2)
G3b: 30–44	0 (0.0)	0 (0.0)	4 (4.4)
G4: 15–29	2 (2.2)	7 (7.8)	0 (0.0)
CKD staging			
CKD stage 1	29 (60.4)	46 (95.8)	47 (98.0)
CKD stage 2	15 (31.25)	2(4.2)	1 (2.0)
CKD stage 3a	4 (8.35)	0 (0.0)	0 (0.0)
CKD stage 3b	0 (0.0)	0 (0.0)	0 (0.0)

Results are presented as frequency and proportion.

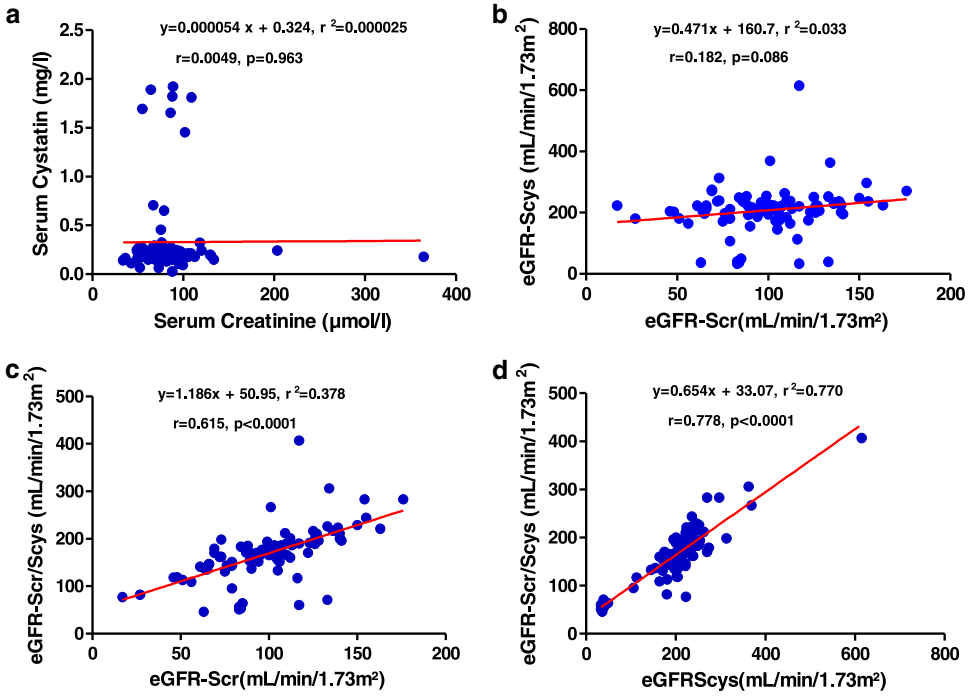

FIGURE 1 | Scatter plot with regression analysis for the comparison of eGFR according to serum cystatin, serum creatinine, and combined Serum Cystatin/serum creatinine equations. (a) Scatter plot with regression analysis for Serum cystatin C and serum creatinine. (b) Scatter plot with regression analysis for eGFR-Scys and eGFR-Scr. (c) Scatter plot with regression analysis for eGFR-Scr/Scys and eGFR-Scr. (d) Scatter plot with regression analysis for eGFR-Scr/Scys and eGFRScys.

Figure 1 shows a linear regression analysis between various eGFR equations. There is a strong positive correlation between eGFR-SCys against eGFR-Cys+SCr ($r = 0.778$, $p < 0.0001$), compared to that between eGFR-SCr against eGFR-Cys+SCr ($r = 0.615$, $p < 0.0001$). The association between SCr and Scys and eGFR-SCr and eGFR-SCys was insignificant ($p > 0.9$, $p > 0.08$, respectively).

Table 3 shows a comparison among CKD-EPI eGFR equations; comparison between eGFR-Cys with eGFR-SCys + SCr (eGFR-Cys vs. eGFR-SCys + SCr) equations had the significant good agreement with the lowest median bias 48.79 and a narrow 95% limit of agreement (kappa = 0.711, p-value < 0.0001, 95% Cl 15.45–97.95). No significant agreement was recorded between eGFR-SCr and eGFR-SCys, and eGFR-SCr and eGFR-SCR + SCys, ($p = 0.4$, $p = 0.6$), respectively.

Bland-Altman plots showed eGFR values about the mean eGFR for the various equations comparisons. The values were concentrated in Figure 1b with a narrow limit of agreement.

Figure 2 shows that the AUC for the eGFR-SCr + SCys was much closer to 1.0 hence the larger AUC and was significant ($p = 0.0001$, AUC = 0.91).

The AUC of an ROC analysis was constructed for eGFR-SCys and eGFR-SCr + SCys to depict a measure of diagnostic accuracy between these two CKD-EPI eGFR equations at similar cut-off values in the prediction of kidney insufficiency of eGFR < 60 mL/min/1.73 m^2 (Figure 2). The eGFR-SCr + SCys had the greatest diagnostic accuracy of a larger AUC (0.9048; $p = 0.001$) and sensitivity of 100% compared to that of eGFR-SCys (AUC = 0.68) without significance (p-value = 0.2) and 83.3% sensitivity (Table 4).

4 | Discussion

CKD is becoming prevalent among HIV/AIDS-infected individuals with kidney dysfunction progressing to ESKD [3, 7]. Thus, we assessed the diagnostic performance of creatinine-based eGFR, cystatin c-based eGFR and combined (creatinine + cystatin c) eGFR equations in diagnosing kidney insufficiency in HIV/AIDS patients on stable ART at the Saltpond District Hospital, Ghana. Our findings showed that the eGFR combined (Scr + Scys) equation has the best diagnostic performance in predicting kidney insufficiency/CKD in HIV/AIDS patients on ART. Serum cystatin c-based estimated glomerular filtration (eGFR-Scr) equation is better for assessing kidney function for patients with eGFR < 60 mL/min/1.73 m^2 and eGFR-Scr based equation is better in eGFR/CKD classification and staging.

Our study revealed a mean serum creatinine level of 82.60 ± 21.69 with serum creatinine level values within the normal range for both female and male participants, which contradicts the findings of Emem et al., [25] where creatinine levels were elevated in a good proportion of HIV/AIDS-patients. The levels of creatinine in our study were significantly ($p = 0.006$) higher in males than females which is at par with the findings of Obirikorang et al. [26]. This variation is accounted for by the increased muscle mass and metabolism in males as compared to females.

TABLE 3 | Comparison of bias, agreement, and accuracy between the CKD-EPI eGFR equations.

Equation	Bias (mL/min/1.73 m²)	95% limit of agreement	SD	*p*-value[a]	Kappa	*p*-value
eGFR_Scr vs. eGFR_Scys	65.50	27.40–103.60	19.44	< 0.0001	−0.077	0.462
eGFR_Scr vs. eGFR_Scr_Scys	87.17	36.51–137.84	25.85	< 0.0001	−0.056	0.585
eGFR_Scys vs. eGFR_Scr_Scys	48.79	15.45–97.95	32.27	0.0161	0.711	< 0.0001

[a]Wilcoxon-matched pairs signed-rank test comparison.

We observed that the eGFR-Scys-based equation was better at assessing kidney function ($p = 0.03$) than eGFR-Scr ($p = 0.6$) and the eGFR combined (Scr + Scys) ($p = 0.1$) based equations.

Muscle mass and metabolism, age, sex, diet, co-morbidities, wasting, sarcopenia, oliguria, etc., among HIV/AIDS patients affect the commonly used creatinine-based eGFR equations in predicting kidney function [21] whereas these factors have little to no effect on the production of cystatin c [27]. Additionally, the ability of the kidney to almost freely filter and completely metabolize cystatin c as compared to creatinine [18] makes the cystatin c-based eGFR equation in our study better in predicting kidney function. Our findings contradict the observation of Mauss et al. [28], in which they indicated that kidney function assessed by creatinine-based eGFR equations was better than that by cystatin c-based eGFR equations in HIV/AIDS patients. Their study employed the MDRD equation for eGFR calculation. However, our study is consistent with that of Patra [29], in which the eGFR-Scys-cre-based equation is better in assessing kidney function in HIV/AIDS patients as compared to creatinine-based eGFR equations only. Our findings are again consistent with those of Mondesert et al. [14] and Mazaheri et al. [30] who concluded that the eGFR-Scys equation should be an additional tool for assessing kidney impairment due to its diagnostic accuracy.

Regarding classification and CKD staging, the combined (Scr + Scys) eGFR equation classified 93% of participants as having eGFR ≥ 60 mL/min/1.73 m^2 whereas eGFR-Scys and eGFR-Scr classified 90% and 92% of participants respectively. However, eGFR-Scys classified 10% of patients with eGFR ≤ 60 mL/min/1.73 m^2 while eGFR combined (Scr + Scys) and eGFR-Scr based equations classified 6.7% and 7.8% of participants, respectively, which is similar to the findings in previous studies [31, 32]. Though no reason could readily be assigned for this observation, our study illustrated that all three eGFR equations are poor in classifications of patients with eGFR ≤ 60 mL/min/1.73 m^2. This finding confirms the report of a study done by Gagneux-Brunon et al. [33] that looked at the performance of MDRD, eGFR-Scr, eGFR-Scys, and eGFR combined (Scr + Scys) based equations in HIV/AIDS patients. They reported that the performance of these equations remains worse in the HIV/AIDS population than the performance observed in the general population. This reduced performance is of particular significance in patients whose eGFR falls below or hovers around 60 mL/min/1.73 m^2.

The regression analysis showed that the strongest correlation was between eGFR-Scys and eGFR combined (Scr + Scys) ($r = 0.778$, $p < 0.001$). Contradicting the studies of Viswanathan et al. [34] in South India, Insignificant correlations were observed between serum cystatin c and creatinine levels or eGFR-Scr and eGFR-Scys. This disparity could be due to the difference in the study population; whereas our study was conducted in HIV/AIDS patients, their study focused on type 2 diabetes mellitus patients.

The current study estimated the diagnostic performance using an ROC plot and combining sensitivity with a specificity of eGFR equations; eGFR (Scr + Scys) whose sensitivity was 100% and specificity was 11% had the greatest diagnostic performance

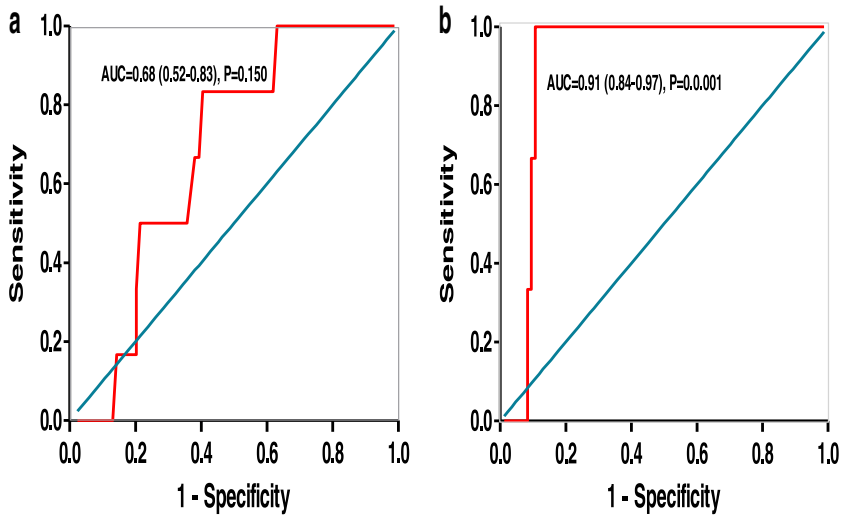

FIGURE 2 | Receiver Operator Curve and Area under the curve (AUC), for CKD-EPI eGFR equations (a) eGFR_Scys and (b) eGFR_Scr_Scys.

TABLE 4 | Diagnostic Performance of the CKD-EPI eGFR equations (eGFR_Scys and eGFR_Scr_Scys) for predicting renal insufficiency (eGFR_Scr < 60 mL/min/1.73 m^2).

Equation	eGFR_Scys	eGFR_Scr_Scys
Cut off value	221.5	222
AUC	0.68	0.9048
95% CI	0.52–0.83	0.84–0.97
Sensitivity (%)	83.3 (35.9–99.6)	100 (54.1–100)
Specificity (%)	42.9 (32.1–54.13)	10.71 (5.0–19.4)
p-value	0.15	0.001

with the largest AUC (AUC = 0.91) in the ROC plot. This to the best of our knowledge is the first study in Ghana to assess the diagnostic performance of eGFR (Scr + Scys) among HIV/AIDS patients. Although there is a difference in the study population, Chi et al. [35] reported in a Chinese diabetic study that eGFR (Scr + Scys) has the highest diagnostic performance with 87.6 sensitivity. Hence, our study reveals that eGFR(Scr + Scys) equations may improve diagnostic efficiency for kidney function at least in the HIV/AIDS population.

Our study was limited by the following:

First, a small sample size and inability to use IDMS standardized creatinine. second, the eGFR equations used have not been validated in the general Ghanaian population, and hence using them in the HIV/AIDS population may not provide the exact eGFR needed to assess kidney function. Finally, we did not determine the relationship between the biomarkers and viral load, lifestyle (diet, exercise, socioeconomic status), and certain co-morbidities as they were not recorded.

5 | Conclusions

The eGFR combined (Scr + Scys) based equation has the best diagnostic performance in predicting kidney insufficiency/CKD in HIV/AIDS patients on ART. Serum cystatin c-based estimated glomerular filtration (eGFR-Scr) equation is better for assessing kidney function for patients with eGFR< 60 mL/min/1.73 m^2 and eGFR-Scr based equation is better in eGFR/CKD classification and staging. Our results show that incorporating cystatin C into the assessment of kidney function in HIV/AIDS patients would enable earlier detection of kidney dysfunction, leading to more timely interventions and improved risk stratification.

Author Contributions

Kweku Amoah Ampiah: conceptualization, formal analysis, visualization, data curation. **Richard Afari:** formal analysis, validation, data curation. **Jude Osei-Assibey:** visualization, data curation. **Ramseyer Asamoah:** visualization, data curation. **Amos Acheampong:** data curation. **Lawrence Dzata:** data curation. **Joseph Kyei-Mensah:** data curation, formal analysis. **Linda Ahenkorah-Fonjo:** formal analysis, writing–review and editing. **Samuel A. Sakyi:** formal analysis. **Albert Abakah-Yawson:** conceptualization, writing–original draft. **Gabriel Pezahso Kotam:** writing–original draft, writing–review and editing. **Richard K. D. Ephraim:** conceptualization, writing–review and editing, formal analysis, visualization, methodology, supervision. All authors have read and approved the final version of the manuscript. The corresponding author and manuscript guarantor had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethics Statement

Ethical approval was obtained from the University of Cape Coast Institutional Review Board and informed written consent was also obtained from the participants.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Transparency Statement

The lead author Gabriel Pezahso Kotam affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. G. Maartens, C. Celum, and S. R. Lewin, "HIV Infection: Epidemiology, Pathogenesis, Treatment, and Prevention," *Lancet* 384, no. 9939 (2014): 258–271.

2. A. Trickey, C. A. Sabin, G. Burkholder, et al., "Life Expectancy After 2015 of Adults With HIV on Long-Term Antiretroviral Therapy in Europe and North America: A Collaborative Analysis of Cohort Studies," *Lancet HIV* 10, no. 5 (2023): e295–e307.

3. A. I. Choi, R. A. Rodriguez, P. Bacchetti, D. Bertenthal, P. A. Volberding, and A. M. O'Hare, "The Impact of HIV on Chronic Kidney Disease Outcomes," *Kidney International* 72, no. 11 (2007): 1380–1387.

4. C. Q. Hoang, H. D. Nguyen, H. Q. Vu, et al., "Determinants of Risk Factors for Renal Impairment Among HIV-Infected Patients Treated With Tenofovir Disoproxil Fumarate-Based Antiretroviral Regimen in Southern Vietnam," *BioMed Research International* 2020 (2020): 1–9.

5. P. J. Peters, D. M. Moore, J. Mermin, et al., "Antiretroviral Therapy Improves Renal Function Among HIV-Infected Ugandans," *Kidney International* 74, no. 7 (2008): 925–929.

6. J. E. Heron, C. I. Bagnis, and D. M. Gracey, "Contemporary Issues and New Challenges in Chronic Kidney Disease Amongst People Living With HIV," *AIDS Research and Therapy* 17 (2020): 11.

7. E. Kwiatkowska, L. Domański, V. Dziedziejko, A. Kajdy, K. Stefańska, and S. Kwiatkowski, "The Mechanism of Drug Nephrotoxicity and the Methods for Preventing Kidney Damage," *International Journal of Molecular Sciences* 22, no. 11 (2021): 6109.

8. K. K. Wools-Kaloustian and S. K. Gupta, "Will There Be an Epidemic of HIV-Related Chronic Kidney Disease in Sub-Saharan Africa? Too Soon to Tell," *Kidney International* 74, no. 7 (2008): 845–847.

9. K. Kalantar-Zadeh, T. H. Jafar, D. Nitsch, B. L. Neuen, and V. Perkovic, "Chronic Kidney Disease," *Lancet* 398, no. 10302 (2021): 786–802.

10. C. A. Fux, M. Simcock, M. Wolbers, et al., "Tenofovir Use Is Associated With a Reduction in Calculated Glomerular Filtration Rates in the Swiss HIV Cohort Study," *Antiviral Therapy* 12, no. 8 (2007): 1165–1174.

11. A. Mocroft, O. Kirk, J. Gatell, et al., "Chronic Renal Failure Among HIV-1-Infected Patients," *AIDS* 21, no. 9 (2007): 1119–1127.

12. C. A. Peralta, R. Katz, M. J. Sarnak, et al., "Cystatin C Identifies Chronic Kidney Disease Patients at Higher Risk for Complications," *Journal of the American Society of Nephrology* 22, no. 1 (2011): 147–155.

13. A. S. Levey, L. A. Stevens, C. H. Schmid, et al., "A New Equation to Estimate Glomerular Filtration Rate," *Annals of Internal Medicine* 150, no. 9 (2009): 604–612.

14. E. Mondesert, J. Reynes, A. Makinson, et al., "Cystatin C in Addition to Creatinine for Better Assessment of Glomerular Renal Function Decline in People With HIV Receiving Antiretroviral Therapy," *AIDS* 37, no. 3 (2023): 447–454.

15. M. J. Perez Elias, B. Alejos, M. M. Gutierrez, et al., "Dynamics of Creatinine Estimated Glomerular Filtration Rate Using One or More Antiretrovirals That Inhibit Creatinine Tubular Secretion," *Journal of Antimicrobial Chemotherapy* 76, no. 4 (2021): 1046–1050.

16. P. M. Beringer, H. Owens, A. Nguyen, et al., "Estimation of Glomerular Filtration Rate by Using Serum Cystatin C and Serum Creatinine Concentrations in Patients With Human Immunodeficiency Virus," *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 30, no. 10 (2010): 1004–1010.

17. H. E. van Deventer, J. E. Paiker, I. J. Katz, and J. A. George, "A Comparison of Cystatin C- and Creatinine-Based Prediction Equations for the Estimation of Glomerular Filtration Rate in Black South Africans," *Nephrology Dialysis Transplantation* 26, no. 5 (2011): 1553–1558.

18. D. C. Chen, O. A. Potok, D. Rifkin, and M. M. Estrella, "Advantages, Limitations, and Clinical Considerations in Using Cystatin C to Estimate GFR," *Kidney360* 3, no. 10 (2022): 1807–1814.

19. X.-R. Zhu, N. Ge, Y. Wang, J. L. Zhai, and C. Liu, "Corticosteroids Significantly Increase Cystatin C Levels in the Plasma by Promoting Cystatin C Production in Rats," *Renal Failure* 41, no. 1 (2019): 698–703.

20. C. Xin, J. Xie, H. Fan, X. Sun, and B. Shi, "Association Between Serum Cystatin C and Thyroid Diseases: A Systematic Review and Meta-Analysis," *Frontiers in Endocrinology* 12 (2021): 766516.

21. L. A. Inker, C. H. Schmid, H. Tighiouart, et al., "Estimating Glomerular Filtration Rate From Serum Creatinine and Cystatin C," *New England Journal of Medicine* 367, no. 1 (2012): 20–29.

22. H. Ali, F. Amoyaw, D. Baden, et al., "Ghana's HIV Epidemic and PEPFAR's Contribution Towards Epidemic Control," *Ghana Medical Journal* 53, no. 1 (2019): 59–62.

23. L. D. Bowers, "Kinetic Serum Creatinine Assays I. The Role of Various Factors in Determining Specificity," *Clinical Chemistry* 26, no. 5 (1980): 551–554.

24. Kit, T.H.C.C.E., Human Cystatin C ELISA Kit.

25. C. P. Emem, F. Arogundade, A. Sanusi, K. Adelusola, F. Wokoma, and A. Akinsola, "Renal Disease in HIV-Seropositive Patients in Nigeria: An Assessment of Prevalence, Clinical Features and Risk Factors," *Nephrology Dialysis Transplantation* 23, no. 2 (2007): 741–746.

26. C. Obirikorang, D. N. M. Osakunor, B. Ntaadu, and O. K. Adarkwa, "Renal Function in Ghanaian HIV-Infected Patients on Highly Active Antiretroviral Therapy: A Case-Control Study," *PLoS One* 9, no. 6 (2014): e99469.

27. S. Hanser, J. Choshi, H. Mokoena, et al., "A Systematic Review Assessing the Potential Use of Cystatin C as a Biomarker for Kidney Disease in People Living With HIV on Antiretroviral Therapy," *Frontiers in Medicine* 11 (2024): 1295217.

28. S. Mauss, F. Berger, D. Kuschak, et al., "Cystatin C as a Marker of Renal Function Is Affected by HIV Replication Leading to an Underestimation of Kidney Function in HIV Patients," *Antiviral Therapy* 13, no. 8 (2008): 1091–1095.

29. S. Patra, "Comparative Study of Significance of Serum Cystatin-C, Serum Creatinine and Microalbuminuria Estimation in Patients of Early Diabetic Nephropathy," *Journal of Diabetes & Metabolism* 06 (2015), http://dx.doi.org/10.4172/2155-6156.1000490.

30. T. Mazaheri, D. Buchanan, R. Hung, et al., "Creatinine and Cystatin C-Based Estimated Glomerular Filtration Rate Estimates of Kidney Function in Black People With HIV on Antiretroviral Therapy," *AIDS* 37, no. 5 (2023): 753–758.

31. L. A. Inker, C. Wyatt, R. Creamer, et al., "Performance of Creatinine and Cystatin C GFR Estimating Equations in an HIV-Positive

Population on Antiretrovirals," *JAIDS Journal of Acquired Immune Deficiency Syndromes* 61, no. 3 (2012): 302–309.

32. C. Y. Jones, C. A. Jones, I. B. Wilson, et al., "Cystatin C and Creatinine in an HIV Cohort: The Nutrition for Healthy Living Study," *American Journal of Kidney Diseases* 51, no. 6 (2008): 914–924.

33. A. Gagneux-Brunon, P. Delanaye, N. Maillard, et al., "Performance of Creatinine and Cystatin C-Based Glomerular Filtration Rate Estimating Equations in a European HIV-Positive Cohort," *AIDS* 27, no. 10 (2013): 1573–1581.

34. V. Viswanathan, C. Snehalatha, M. Nair, and A. Ramachandran, "Comparative Assessment of Cystatin C and Creatinine for Determining Renal Function," *Indian Journal of Nephrology* 15 (2005): 91.

35. X. H. Chi, G. P. Li, Q. S. Wang, et al., "CKD-EPI Creatinine-Cystatin C Glomerular Filtration Rate Estimation Equation Seems More Suitable for Chinese Patients With Chronic Kidney Disease Than Other Equations," *BMC Nephrology* 18, no. 1 (2017): 226.